Quinine Sulfate in the Management of Nocturnal Leg Cramps
White Paper and Criteria for Nonformulary Use

VHA Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel/VA Med Safe

Summary and PBM/MAP Recommendations for Nonformulary Use of Quinine for Nocturnal Leg Cramps

There is conflicting evidence for the benefit of quinine in the management of nocturnal leg cramps, however the risk for serious adverse events, although rare, is well known. Because of the known risks and questionable benefit, the FDA (in 1994) found the use of quinine for the treatment of leg cramps to be an unfavorable treatment and have recommended cessation of its use in this benign medical condition. Other pharmacologic treatments cannot necessarily be recommended since they have not been found to be helpful or have been inadequately studied.

1. The PBM/MAP requests clinicians, who have patients currently receiving quinine for leg cramps, to discuss the benefits and risks of continuing quinine with their patients. (Quinine is still available as a prescription product for the treatment of malaria and is available in certain tonics and dietary supplements). There are still many patients who are using quinine for treatment of their leg cramps (see Appendix 1 for VA usage data). Documentation of this reevaluation and discussion with the patient is highly recommended.
2. For patients whose quality of life is severely affected by nocturnal leg cramps and who have not responded to other modalities (physical maneuvers, etc.), a 4-week trial of quinine may be considered with appropriate patient education and close monitoring for both effectiveness and adverse events. Documentation of this discussion with the patient is highly recommended.

Background

Nocturnal leg cramps can be defined as sudden, painful, involuntary maximal contraction of a muscle or a group of muscles lasting up to 10 minutes in a person with no other neurological or muscle pathology.[1] The cramps most commonly affect the muscles in the lower limbs namely the calf muscle but can involve other muscles. Leg cramps recurring in patients without vascular disease are referred to as idiopathic leg cramps. They often disrupt sleep and typically occur within the first few hours of falling asleep. They are more common in middle aged or older people, those with asymptomatic peripheral vascular disease and pregnant women. Their occurrence is generally unpredictable either occurring intermittently or on a nightly basis. Nocturnal leg cramps may be a painful symptom of a benign etiology or a presenting symptom of an underlying disease [2] (see table 1).

Table 1. Possible causes of leg cramps

Congenital	McArdle's disease (glycogen storage disease), autosomal dominant cramping disease
Endocrinologic	Thyroid disease, diabetes mellitus, Addison's disease
Fluid and electrolyte disorders	Hypocalcemia, hyponatremia, hypomagnesemia, hypokalemia and hyperkalemia, chronic diarrhea, hemodialysis
Neuromuscular disorders	Nerve root compression, motor neuron disease, mononeuropathies, polyneuropathies, dystonias
Vascular disorders	Peripheral vascular disease
Toxins	Lead or strychnine poisoning, spider bite
Drugs	Calcium channel blockers (nifedipine), diuretics, phenothiazines, fibrates, selective estrogen receptor modulators (raloxifene), ethanol; morphine withdrawl
Occupational	Focal dystonias; commonly develop writers, athletes, miners, and musicians
Other	Diarrhea, liver cirrhosis, chronic alcoholism, sarcoidosis

Leg cramps are common in older people. Abdulla, et al. [4] conducted an in-depth survey of 365 outpatients aged 65 years and older to determine the prevalence of leg cramps in this population. They found that 50% of patients reported cramps. Cramps were more common in women (56%) than in men (40%) and most were reported to occur at night (62%). Authors of another study surveyed 515 veterans at the Denver VAMC. They found that 56% of veterans surveyed experienced nocturnal leg cramps. In those veterans reporting daily cramps, the majority (82%) had reported them to their provider. In those patients experiencing cramps 1-12 times per year, only 37% reported them. Of the patients with daily cramps, 55% received treatment with the majority taking quinine and reporting the most benefit from quinine. Other treatments were diazepam, vitamin E, amitriptyline, phenytoin and diphenhydramine with no patients describing these agents as being effective.[5]

For decades, quinine sulfate has been the most common therapy for the management of nocturnal leg cramps. However, over the last decade, there has been significant concern regarding its unfavorable risk to benefit profile for the treatment of benign nocturnal leg cramps. In 1994, the FDA banned OTC marketing of quinine for the prevention and treatment of nocturnal leg cramps.[6] They did so because of an absence of evidence of quinine's effectiveness in treating this condition and risk of adverse events at doses used to treat cramps. These risks were believed to outweigh quinine's potential benefit for this non life-threatening condition. From 1969 through June 1992, one hundred and fifty-seven reports of side effects related to quinine use were reported to the FDA. These adverse effects included sight disturbances, dizziness, cinchonism (nausea, vomiting, tinnitus, and deafness) fever, diarrhea, thrombocytopenia and 23 reports of death. After further review, the FDA halted OTC marketing of quinine for malaria in 1998.[7] Quinine is still available as a prescription product for the treatment of malaria but has no indication for treating leg cramps. It is available OTC in certain tonics and dietary supplements. In this white paper, the effectiveness and safety of quinine for the management of nocturnal leg cramps will be reviewed and recommendations for use will be made.

Evidence for Efficacy of Quinine in the Management of Nocturnal Leg Cramps

The exact mechanism for quinine's potential benefit in treating leg cramps is not entirely known, however there are three proposed mechanisms contributing to its activity in this condition. First, it increases the refractory period of skeletal muscle contraction by direct action on the muscle fiber. Second, it decreases the excitability of the motor end plate, an action similar to that of curare. And third, it affects the distribution of calcium within the muscle fiber.[20]

In 1995, a meta-analysis of six randomized, double-blind, crossover trials examining quinine's effectiveness in managing nocturnal leg cramps was published.[8] The six included trials had a combined total of 107 patients reporting more than 2 leg cramps per week. The dose of quinine ranged from 200-500 mg daily. The authors noted a reduction in the frequency of cramps with quinine compared to placebo (8.83 fewer cramps, 95% CI 4.16-13.49) over a 4-week period. However, the severity and duration of the cramps was not altered with quinine vs. placebo. The authors of this meta-analysis concluded that quinine effectively reduced the frequency but not the severity or duration of leg cramps. However in light of the serious safety concerns, patients receiving such therapy should be closely monitored.

In 1998, the same authors conducted a second meta-analysis of quinine's effectiveness in reducing leg cramps. This time including data from four published and four unpublished trials.[9] Included trials were randomized, double blind, and placebo controlled. All but one trial used a crossover design for a combined total of 409 patients. With the inclusion of the unpublished data, the magnitude of benefit from quinine over a 4-week period was reduced to 3.6 fewer cramps (95% CI 2.2-5.1) vs. placebo. There was also a reduction in severity of cramping with quinine vs. placebo (95% CI 0.05-0.21, p=0.0023). In this analysis, more subjects taking quinine experienced adverse effects and withdrew from treatment than those on placebo. Tinnitus was the adverse event reported more often in users of quinine versus placebo. The authors concluded that quinine is an effective treatment for nocturnal leg cramps although the magnitude of the benefit was reduced by addition of high-quality data from unpublished trials. However, in light of the short-term adverse event risk of quinine, the authors recommend nonpharmacologic techniques (e.g. regular passive stretching of the involved muscles[10]) be tried prior to pharmacologic treatments. However, if a

patient's quality of life is severely affected by their condition, a 4-week trial of quinine may be considered with appropriate patient education and monitoring for both effectiveness and adverse events.

Other published trials have examined quinine's efficacy in reducing nocturnal leg cramps and not all of the data support quinine's benefit in reducing cramps (see table 2). Some authors have attempted to explain the reason for the conflicting results of the studies including small sample size, varied study duration (1-4 weeks) and the primary outcome measure of frequency, severity and duration of leg cramps is purely subjective and may alter study results. In addition, studies demonstrating greater benefit were more likely to be published than those finding less benefit from quinine.

Table 2. Published Studies of Quinine For Reducing Leg Cramps in Non-Dialysis Patients

STUDY	DESIGN	N	INCLUSION	DRUG	DOSE	DURATION	RESULTS	4 WEEK CRAMP BENEFIT*
Jones et al[11]	rdbpc, crossover	9	≥2 cramps/week	quinine sulfate	300 mg hs	2 weeks	p<0.01	-4.0
Waburton et al[12]	rdbpc, crossover	22	>2 cramps/week	quinine bisulfate	300 mg hs	3 weeks	NS	-4.06
Fung et al[13]	rdbpc, crossover	8	>2 cramps/week	quinine sulfate	200 mg hs	4 weeks	p<0.01	-7.37
Connolly et al[14]	rdbpc, crossover	27	≥6 /month	placebo, vitamin E, or quinine sulfate	500 mg pm	4 weeks	p=.0046	-17.56 vitamin E had no effect
Siderov[15]	rdbpc, crossover	16	>2 cramps/week	quinine sulfate	200 mg hs	2 weeks	NS	-1.37
Dunn[16]	rdbpc, crossover	25	quinine use	quinine sulfate	300 mg hs	4 weeks	31% (# n/a) fewer cramps p<0.01	n/a
Jansen[17]	rdbpc parallel	102	≥3 cramps/week	hydroquinine	300 mg q pm	2 weeks	36% or 8 fewer cramps (95%CI7-12)	n/a
Diener[18]	rdbpc, parallel	98	>6 in 2 weeks (average of 12)	quinine	400 mg	2 weeks	8 fewer cramps (95%CI7-10)	n/a
Woodfield[40]	N of 1 study rdbpc crossover	10	4 or> in 2 weeks	Quinine	200-300 mg	3-4 week periods with quinine crossover to placebo	Quinine reduced cramps in 3 patients (P<0.05), 6 reported nonsignificant reduction in cramps, 1 no change	n/a. Despite effect on cramps, all patients chose to continue quinine.

rdbpc=randomized, double-blind, placebo-controlled
*Calculated in Man Son Hing meta-analysis by obtaining further individual patient data and doubling 2-week data to standardize to a 4–week treatment period. (table adapted from 2002 Quinine document)

The Cochrane Collaboration has published a protocol for a planned systematic review for the safety and efficacy of quinine for muscle cramps.[19] The review will contain new studies conducted since the 1998 meta-analysis and analyze relevant outcomes assessing the efficacy of quinine type agents in the management of leg cramps. Although this review will be helpful, it is not yet completed.

Adverse Events of Quinine

Quinine has been used since the 1940's for the relief of nocturnal leg cramps. It has been suggested that since quinine has been around for so many years that many physicians underestimate its risk for adverse events.[20]

Quinine is known to be associated with serious adverse events including potentially life-threatening hypersensitivity reactions, notably quinine-induced thrombocytopenia. The FDA has estimated that between 1:1000 and 1:3500 users may experience thrombocytopenia from quinine. This reaction is unpredictable and can occur after only a single dose or after months or years of use. Other serious hypersensitivity adverse events may include angioedema, pancytopenia, hemolytic uremic syndrome, and intravascular coagulation.[20]

In 2001, authors report that 11% of 132 consecutive patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome or TTP-HUS (in central western Oklahoma's TTP-HUS registry) since July of 1995 were associated with quinine.[21] The authors describe quinine's toxicity as immune-mediated with an explosive onset, and all patients reported quinine use for nocturnal leg cramps on and off for many years. Of note, all the patients were women. In a second article the same group compiled the clinical features of 39 previously reported cases of quinine induced TTP-HUS, including the initial cases by Gottschall et al.[22] that established TTP-HUS as a new clinical entity. Of the cases, 87% were women, and a common presentation in all the cases was chills and fever with abdominal pain, nausea, vomiting, diarrhea, and oliguria.[23] They also make a case for the urgent diagnosis of TTP-HUS, citing a remission rate of over 80% for patients receiving prompt treatment, versus a 90% fatality rate prior to the availability of plasma exchange for immediate treatment. There are reports of repeated episodes of TTP-HUS in patients who took quinine on different occasions [24]; therefore any patient with a history of immune mediated thrombocytopenia or G-6-PD deficiency should not be given quinine. A complete database describing all of the above referenced group's case reports can be found at http://moon.ouhsc.edu/jgeorge. Of note, the majority of these cases occurred in women. From a survey discussed early in this report[4], more women reported leg cramps than men and TTP is believed to occur more commonly in women as well. As a result, it is difficult to determine whether quinine-induced isolated thrombocytopenia occurs more commonly in women than in men.

Another group of investigators reviewed spontaneous reports to the FDA of isolated thrombocytopenia associated with quinine and identified 64 cases that were believed to be related. Sixty-six percent of cases were reported in females and 34% in males. In their report, they determined that the onset of symptoms was rapid in the subset of patients they reviewed. The authors encourage physicians to conduct an adequate history for ingestion of quinine in patients with thrombocytopenia and an in depth food/dietary supplement history for possible ingestion of foods/tonic waters/supplement products containing even small amounts of quinine.[25]

Other reported adverse effects may include cinchonism, which is a condition presenting with tinnitus, visual disturbances, headache, vertigo, nausea and vomiting, and deafness. In cases of quinine toxicity, there have been reports of permanent blindness, convulsions, acute renal failure and death.[19, 26]

Quinine is the optical isomer of quinidine and at higher serum levels quinine may interfere with cardiac conduction pathways leading to cardiac arrhythmias and death.

Finally, there is at least one reported case of reversible pulmonary infiltrates possibly induced by quinine.[27]

The pharmacokinetics of quinine may be altered in those with renal or hepatic function and also in older persons. Because of this, the frequency of adverse events may be increased in older patients. In addition, there are known drug-drug interactions with quinine (see table 3).

Table 3. Drug-Drug Interactions with Quinine

DRUG	EFFECT	CONSIDERATIONS
Aluminum-containing antacids	↓ Quinine	Aluminum-containing antacids decrease the absorption of quinine.
Quinine	↑ Oral anticoagulants	Quinine may enhance the effects of warfarin and other oral anticoagulants by depressing the hepatic synthesis of vitamin k dependent clotting factors.
Cimetidine	↑ Quinine	Cimetidine may decrease the elimination of quinine and cause toxicity.
Quinine	↑ Digoxin	Increased levels of digoxin have been found with quinine administration; digoxin levels should be monitored in patients taking this combination.
Mefloquine	↑ Quinine	Mefloquine and quinine use can cause ECG abnormalities and cardiac arrest.
Quinine	↑ Neuromuscular blocking agents	Neuromuscular blocking agents (depolarizing and nondepolarizing) may be potentiated and cause respiratory problems.
Quinine	↑ Succinylcholine	Quinine may decrease cholinesterase activity, slowing the metabolism of succinylcholine.
Rifamycins	↓ Quinine	Rifamycins increase the clearance of quinine.
Urinary alkalinizers	↑ Quinine	Urinary alkalinizers (acetazolamide, sodium bicarbonate) may increase quinine blood levels and cause toxicity.
Azole Antifungals	↑ Quinine	Inhibition of quinine's metabolism
Quinine	↑ Carbamazepine	Quinine may increase carbamazepine levels
Rifampin	↓Quinine	Reduce quinine levels

Quinine has a long half-life, is protein bound, and metabolized by the cytochrome P450 system; therefore careful monitoring for drug interactions as well as hepatic or renal impairment is justified.
Adapted from Drug Facts and Comparisons, January 2006.[28]

As noted above, there are conflicting data for the benefit of quinine in reducing nocturnal leg cramps. This is complicated by the fact that there are known serious adverse events associated with the use of quinine in doses used for treating cramps. The Cochrane Collaboration stated in their quinine protocol "S*ustained clinical use of this potentially harmful drug in the alleviation of an essentially benign condition such as muscle cramps can therefore only be justified if medical efficacy and safety are indisputable"*. Because of the known risks and questionable benefit, the FDA found the use of quinine for the treatment of leg cramps to be an unfavorable treatment and have recommended cessation of its use for this benign condition.

Alternatives to Quinine For Nocturnal Leg Cramps

Pharmacologic Alternatives

Vitamin E

To date, there have been two uncontrolled, early reports of a serendipitous finding that administration of vitamin E significantly reduced the frequency of leg cramps in a group of 125 patients.[29, 30] About 50% received 300 IU or less and the other 50% received 400 IU or more.

A subsequent randomized, double-blind, placebo-controlled, crossover trial compared vitamin E to quinine in 27 male veterans who reported at least 6 cramps per month. All patients received quinine 200 mg in the morning and 300 mg at bedtime, vitamin E 800 IU, or placebo for 4-week periods in random order. Each period was separated by a 4-week washout. Compared to placebo, patients receiving quinine experienced a lower frequency of cramps and sleep disturbances ($p=0.0046$). There was no difference in cramp severity. In those receiving vitamin E, there was **no** reduction in frequency of cramps or sleep disturbances or cramp severity compared to placebo.[14]

A final study, using a double-dummy design, compared quinine 325 mg to vitamin E 400 IU at bedtime to determine efficacy in reducing dialysis leg cramps. The study included a two-month washout period followed by a two-month treatment period. During the washout phase, there were approximately 10.9 cramps reported per month from those to receive quinine and 10.4 cramps reported per month from those to get vitamin E. During the first month, those receiving quinine had a one-month reduction in cramps to 3.6 compared to 3.3 for the vitamin E group ($p<0.0005$ for both groups combined from baseline). The reduction in frequency of cramps was maintained throughout the second month of the active treatment period. The authors concluded that because of the safety concerns surrounding quinine and similar benefit in cramp reduction with vitamin E in these patients, vitamin E should be tried first. Limitations of this

study include no placebo control and data were analyzed on only the 29 patients completing the study (not intent to treat).[31]

In a meta-analysis published early in 2005, investigators observed an increase in all-cause mortality in those users of high-dose vitamin E (≥400 IU/day) versus control or placebo.[41] As a result, the evidence for the benefits and risks of vitamin E for this condition should be considered.

Verapamil
In an uncontrolled trial involving eight patients with leg cramps refractory to quinine, seven patients reported a reduction in their cramping with verapamil 120 mg at bedtime.[32] There are no controlled trials examining the effect of verapamil in patients with leg cramps.

Magnesium Salts
Although there are some data to support the use of magnesium salts for treating leg cramps in pregnant women [33, 34], two other trials conducted in nonpregnant individuals failed to show a benefit of magnesium versus placebo.[35, 36] In the study by Roffe et al,[36] patients did report an overwhelming preference for magnesium as opposed to placebo. Some individuals receiving magnesium reported diarrhea.

Nonpharmacologic Interventions

Although nonpharmacologic or physical maneuvers have not been adequately evaluated in controlled clinical trial settings, they may be worthwhile for some patients.[37] These interventions include loosening up the covers over the feet so the feet can maintain dorsiflexion during rest. In addition, passive stretching of the calf muscles several times daily has been observed in an uncontrolled setting to reduce the frequency of cramping.[38] Another controlled trial did not show a benefit of calf stretching exercises while quinine cessation was attempted.[39] Also drink adequate amounts of water to maintain hydration. Patients experiencing cramps should be educated that when cramping occurs, try to stretch the affected muscle or group of muscles by straightening the leg and flex the foot toward the knee. Tell them to grab their toes and gently pull them toward their knees. The muscles can also be gently massaged to help them relax.[37]

Summary and PBM/MAP Recommendations for Use of Quinine for Nocturnal Leg Cramps

There is conflicting evidence for the benefit of quinine in the management of nocturnal leg cramps, however the risk for serious adverse events, although rare, is well known. Because of the known risks and questionable benefit, the FDA (in 1994) found the use of quinine for the treatment of leg cramps to be an unfavorable treatment and have recommended cessation of its use in this benign medical condition. However, from the available data, some patients do benefit from quinine in terms of less cramping. In addition, several reports, describing quinine induced thrombocytopenia, observed the adverse event to occur primarily in women. Other pharmacologic treatments cannot necessarily be recommended since they have not been found to be helpful or have been inadequately studied.

1. The PBM/MAP requests clinicians, who have patients currently receiving quinine for leg cramps, to discuss the benefits and risks of continuing quinine with their patients. (Quinine is still available as a prescription product for the treatment of malaria and is available in certain tonics and dietary supplements). There are still many patients who are using quinine for treatment of their leg cramps (see Appendix 1 for VA usage data). Documentation of this reevaluation and discussion with the patient is highly recommended.

2. For patients whose quality of life is severely affected by nocturnal leg cramps and who have not responded to other modalities (physical maneuvers, etc.), a 4-week trial of quinine may be considered with appropriate patient education and close monitoring for both effectiveness and adverse events. Documentation of this discussion with the patient is highly recommended.

Update prepared by Cathy Kelley, Pharm.D.

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Appendix 1.

QUININE*

	FY2005 Through August	
VISN	**Unique Patients**	**Dose/Day**
01	3,183	348.32
02	1,058	341.22
03	598	351.83
04	1,756	302.61
05	337	328.75
06	3,236	328.96
07	370	360.64
08	2,268	335.83
09	162	341.95
10	2,394	333.69
11	3,728	333.6
12	2,578	337.28
15	3,818	350.98
16	3,518	345.82
17	176	303.22
18	3,966	359.24
19	2,857	345.86
20	4,529	350.91
21	162	294.42
22	1	1,950.00
23	3,750	318.99
Nation	**44,226**	**340.04**

*** Includes:**

QUININE SO4 200MG CAP
QUININE SO4 260MG TAB
QUININE SO4 325MG CAP